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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,346	URTHALER ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9,11-20,23,24,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-9, 11-20, 23, 24, 40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 12/21/07. The previous rejection have been overcome and the following rejections and objections are presented. Claims 2-9, 11-20, 23, 24, 40 and 41 are under examination in this application.

Claim Objections

Claims 40 and 3-6, 11, 13 and 41 are objected to because of the following informalities: Claim 40 recites in the preamble "method of producing a biomolecule" whereas the method is not actually drawn to producing a biomolecule, a host cell is used that produces a biomolecule. Rather, the claim is directed to methods of purifying a biomolecule from a host cell.

In line 4, the claim recites "optionally harvesting and re-suspending the cultivated host cells". However, this step cannot be optional as in step b) the method requires "introducing the cell suspension" into a lysis reactor. It would be remedial to delete the word "optionally" and amended step a) to recite --wherein a cell suspension is produced-- to provide adequate antecedent basis for the phrase "the cell suspension".

In line 9, the claims refer to "the alkaline lysate and precipitating cellular debris and impurities" presumably resulting from use of alkaline lysis in step b). It would be remedial to amend step b) to recite --wherein an alkaline lysate with precipitating debris and impurities is produced-- thus providing adequate antecedent basis. In claim 15, the phrase "the lysed cell solution' should coordinately be amended to be consistent with this amendment.

It is also noted that in step b) that the lysis reactor and the alkaline lysis reactor appear to be the same but use of the distinct terms implies that there are two reactors. This can be clarified

by either using the same term for both or by indication in the claim of --further lysis by alkaline lysis in an alkaline lysis reactor--.

Claim 40, line 12 and claim 15 recites "a neutralization reactor" whereas it is proper to refer to terms previously recited using the article "the" to distinguish from newly recited limitations. In this case, it would be remedial to amend line 10 to --the neutralizing reactor--.

Claim 40, step d) refers to "neutralized lysate containing the biomolecule of interest" which is presumably created from step c). For clarification, it would be remedial to amend step c) to recite --wherein a neutralized lysate is produced comprising the biomolecule of interest --.

Claim 40, step e) recites "purifying the biomolecule of interest". For completeness,. it would be remedial to recite that the biomolecule is purified from the purified lysate.

Claims 3-6, 40 and 41 refer alternatively to "the retention material" and "the retention layer". It would be remedial to amend the claims to refer to the same term using the same terminology. In this case, claim 40 references "a retention material" and hence it would be preferable to amend the claims to reference solely --the retention layer--.

The recitation in claims 3 and 5 "composed of" would be preferable as --comprises--.

In claim 5, "rigid retention material" requires the article --a--.

Claim 11 would be preferable if amended to recite --thus forming a single flow within the lysis reactor--.

Claims 13 and 14 recite "said two flows". When using the term "said" the phrase following should be an exact recapitulation of the previously recited term. If not, the term --the-- is more appropriately used. In this case, the previous limitations is "two independent flows" and therefore claim 13 should reference these by recitation --the two flows--.

Claim 41 recites the phrases "a mixture of precipitate and lysate" obtained in step c). For consistency and accuracy, It would be remedial to amend claim 41 to recite --the lysate with precipitating debris and impurities--. Use of the article "a" often reference newly recited limitations and the reference to a lysate and precipitate appears to be reference to a previously recited limitation. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 5, 9, 11-20, 23, 24, 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 recites the limitation "the lysis solution" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 recites the limitation "the neutralizing solution" in line 12. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 recites the limitation "the method is drawn to several types of lysate and it is not clear to which of these line 17 refers.

Claim 40 is vague and indefinite in that the metes and bounds of "the top" when referring to a portion of the "retention material" are unclear. However, there is no orientation indicated in the claim such that a person of skill in the art would know to what the top refers.

Claim 2 recites "the lysate contains the biomolecule of interest" in claim 40. There is insufficient antecedent basis for this limitation in the claim. Claim 40 is drawn to several types of lysate and it is not clear to which of these claim 2 refers. It is noted that claim 40 already recites that the neutralizing lysate comprises the biomolecule of interest and so thus it appears that claim 2 does not further limit claim 40.

Claim 7 recites the limitation "the mixture from the top of the clarification reactor" in claim 40. There is insufficient antecedent basis for the limitation "the mixture" as well as "the top" in the claim. Claim 7 is directed to the clarification step but it is not clear what is encompassed by neither "the mixture" nor what the "top of the clarification reactor" is as the clarification reactor is not designated with orientations.

Claim 7 recites "the lysate " in claim 40. There is insufficient antecedent basis for this limitation in the claim. Claim 40 is drawn to several types of lysate and it is not clear to which of these claim 7 refers.

Claim 11 which recites "the alkaline lysis solutions" in claim 40. There is insufficient antecedent basis for this limitation in the claims.

Claim 24 recites the limitation "the host cells obtained in step a)" in claim 40. however there is insufficient antecedent basis for the limitation of obtained host cells in step 1). Furthermore, it is not clear when the cells are cryo-pelleted, prior to or during the cultivation.

Claim 41 recites the limitation "the surface of the retention layer" in line 17. There is insufficient antecedent basis for this limitation in the claim. As well in this claim the phrase "to reach" is unclear as it is not clear what is needed "to reach" the surface of the retention layer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 3, 5, 9, 11-20, 23, 24, 40 and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Nochumson (US 20060106208; see entire document). **This is a new rejection.** Nochumson et al teach methods of purification of biomolecules using automated and semi-automated continuous units, which given the broadest interpretation can be considered reactors as the described reactions are undertaken in these units. As demonstrated in figure 2 and described in ¶ 0041, the cell suspension is loaded and undergoes alkaline lysis following which neutralization occurs. Following this, the lysate is clarification from a precipitated cellular debris and impurities (RNA, chromosomal DNA, endotoxin, denatured plasmid). In these steps, the DNA flows through while the impurities remain in the column. The method is performed on a continuous, flow-through device (see e.g. 0019) in which resuspended cells, lysis solution and neutralization solutions are mixed using continuous flow, in line. Nochumson et al teach that lysis solution and cells can either be combined without further mixing prior to entering the lysis reactor (see e.g.0055) or else can be introduced into the lysis reactor and combined for example by use of an impeller mixer (see e.g. ¶ 0036). In the case that the two are part of two independent flows that are mixed in the lysis reactor, one of skill in the art would recognize that these flows would reasonable make a single flow to an inline static mixer by use of a T or Y

shaped connector these being configurations that would lead to a single flow (see e.g. ¶ 0055 and figure 1). Effluent from the lysis reaction was directed to neutralization which Nochumson et al teaches occurs by flowing lysate and neutralization solution through an inline state mixer in a continuous mode wherein a continuous flow indicates that flow is constant (see e.g. ¶ 0080).

The lysate is clarified and this is said to occur by a variety of techniques known to those of skill in the art (see e.g. ¶ 0072-0073 and 0063). This occurs through fluid connections between the units (see e.g. ¶ 0019-0021 and 0054). As well pumps are used to distribute the lysate and mixtures throughout the method. Claim 24 recites that the cells at step a) are cryo-pelleted. It is understood that this intends that the cells prior to use are cryo-pelleted. Nochumson et al teach that the cells can be frozen prior to use in the lysis reaction (see e.g. ¶ 0078) and in the broadest interpretation, these can be cryo-pelleted cells. Nochumson teaches that clarification occurs for example following alkaline lysis and neutralization by separation of the precipitated impurities by subsequent chromatographic steps (see e.g. ¶ 0048). The chromatographic step uses reactors comprising particulate material. Several wash steps are included as is clarification and concentration (see e.g. ¶ 0050-0053).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5, 9, 12-20, 23, 24, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson (US 20060106208; see entire document) in view of Craig (U.S. Patent No. 6,381,967; see entire document). **This is a new rejection.**

Applicants claim a method to purify a biomolecule of interest wherein a cell mass obtained by cultivating host cells to produce the biomolecule are cryo-pelleted.

The teachings of Nochumson et al are as above. While, Nochumson teaches that the cells are frozen, there are specific means of cryo-pelleting that Nochumson does not teach.

Craig teaches problems that cause cell death during cell freezing, including death due to formation of large sharp ice crystals, and also cell poisoning due to osmotic dehydration by formation of ice crystals. Craig teaches that freezing can involve a process of vitrification, which is the solidification of solutions at low temperature without ice crystal formation. Craig teaches that the higher the speed of the temperature change, the lower the viscosity required to vitrify and faster freezing rates lead to smaller ice crystals (see column 1, lines 16-44, for example). Craig teaches that the goal of any cryopreservation process is to minimize cell damage (see column 2, lines 1- 30, for example). Craig teaches a freezing method in which a liquid sample is transformed into small drops that are directly contacted with a partially solidified refrigerant. Craig teaches that this method is useful for substances that are susceptible to ice crystal or osmotic damage such as cells, plant material, tissue culture cells, sperm and embryos (see column 3, lines 20-25, column 4, lines 29-40, and column 12, lines 9- 20, see, for example).

It would have been obvious to the skilled artisan at the time the invention was made to use the rapid freezing method as taught by Craig to form bacterial cell cryo- pellets for storage prior to a method of biomolecule purification as rendered obvious by QIAGEN and Santoro et al

because QIAGEN suggests that the harvested bacterial cells can be frozen before use and Craig teaches an advantageous method of freezing cells. The motivation to freeze the bacterial cells by dropping them into partially solidified gas to form a cryopellet is the expected benefit of freezing the cells quickly in order to avoid formation of damaging and cytotoxic ice crystals as taught by Craig. There is a reasonable expectation of success to cryopellet bacterial cells before use since this has worked previously as taught by Craig. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 2-9, 11-20, 23, 24, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson (US 20060106208; see entire document) in view of Marquet et al (U.S. 5,561,064; see entire document) or Gonzalez et al (U.S. 5,783,686; see entire document). **This is a new rejection.**

Applicants claim a method to purify a biomolecule of interest wherein a cell mass obtained by cultivating host cells to produce the biomolecule are clarified using glass beads or sinter plates.

The teachings of Nochumson et al are as above. While, Nochumson et al teach that lysates produced by alkaline lysis and neutralization are also clarified, Nochumson et al do not teach that the filtrations utilize glass beads or sinter plates.

The are is replete with methods for clarification of plasmid DNA as well as other biomolecules in which lysates are clarified from impurities are filtered through sinter plates or

glass beads. Gonzalez et alt each that purification systems rely upon the ability of DNA to bid not the surfaces of glad or glass beads. Marquet et al teach advances in filtration devices for purification of biomolecules. The filtration devices are scalable. remove contaminants, do not rely upon addition of extraneous proteins such as RNAse, organic extractants or mutagenic reagents (see e.g. bridging ¶ col 2-3). Marquet et al teach that cell debris and impurities can be removed from the lysate containing DNA by filtration through a material that is porous enough for plasmid DNA to pass through, but not insoluble material. Marquet et al teach that the filter device can be comprised of a porous fritted glass disks (see e.g. col 8, line 23-50). This method requires application of pressure for example which requires that pressure be placed above the filter to force outflow of the lysate and functions as a distribution means to force the lysate to reach the retention layer.

As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Exparte Smith --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, it would have been obvious to the skilled artisan at the time the invention was made to use the filter systems as taught by Gonzalez et al and Marquet et al in the methods of Nochumson et al because Gonzalez and Marquet et al teach that using glass discs as well as glass beads was well known in the art and could be used in scale up methods and because Nochumson et al teaches that a variety of methods for DAN clarification could be used in methods of large scale purification of DNA. As well, it is within the ordinary skill of the art to use available methodologies to purify DNA and one would have been motivated to do so in order as the ability to modify filtration systems by applying conventional methodologies was well known in the art.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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